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(54) **METHACOLINE OR HISTAMINE FORMULATIONS FOR DETECTING ASTHMA**

METHACOLINE ODER HISTAMINE FORMULIERUNGEN ZUR FESTSTELLUNG VON ASTHMA

FORMULATIONS A BASE DE METHACOLINE OU D'HISTAMINE POUR DETECTER L'ASTHME

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to improved formulations for use in detecting asthma, a method of preparing the new formulations and use of the new formulations in the manufacture of a preparation for detecting asthma. Preferably the formulations contain methacholine or histamine as the active ingredient.

BACKGROUND OF THE INVENTION

[0002] Asthma is a common respiratory disease affecting 5-10% of the population. It is characterized by shortness of breath, cough, airway inflammation and hyper-responsiveness to many stimuli. The diagnosis of asthma is based on the clinical history, physical examination and a number of laboratory tests. A key lab test to diagnose non-specific bronchial hyper-responsiveness is the methacholine challenge.

[0003] The methacholine challenge (MC) is the principal test that is used to measure bronchial hyper-responsiveness and hence is a key laboratory test used in the diagnosis of asthma. Methacholine is a bronchoconstrictor which causes a greater degree of airway narrowing in patients with asthma compared to non-asthmatics. The patient's pulmonary function (e.g. FEV1) is measured after each dose until the drop in pulmonary function exceeds a certain degree (e.g. 20% drop in FEV1), or a maximal dose of MC has been given. However, the widespread use of the MC is limited for a number of reasons including:

1. MC is technically difficult to perform: (a) The test is performed by having the subject inhale up to about 10 different concentrations of methacholine (usually doubling doses) via a nebulizer. The methacholine is in solution and a technician has to prepare the different concentrations. This is time consuming, is prone to error and is thus costly. (b) The equipment required is relatively cumbersome, for example, the nebulizer requires a compressor or a compressed gas tank. Furthermore, this equipment is not disposable and thus it has to be cleaned and sterilized after each use. In addition, the output of the nebulizer has to be checked on a regular basis. (c) To deliver the correct amount of methacholine that is inhaled requires some device attached to the nebulizer (e.g. a dosimeter). All of these issues makes the performance of a MC relatively difficult, such that the test is usually performed in a fully equipped laboratory and not in a physician's office. In addition, because of the equipment required, it is not suitable for mass screening of patients.
2. Quality control: Because of the need to prepare various solutions of methacholine, there is the possibility of errors in preparation of the solutions, and errors in the order of administration of the correct doses.
3. Safety: Because of the possibility of errors in preparation of the solutions, a patient may receive too high a dose and this may lead to severe bronchoconstriction.

[0004] In view of the foregoing, there is a need in the art for a method for detecting asthma which overcomes the difficulties described above.

SUMMARY OF THE INVENTION

[0005] The present invention provides improved formulations for use in detecting asthma. The novel formulations provide methacholine or histamine in ready to use powder formulations which can be inhaled directly through an inhaler in order to test for air narrowing which is diagnostic of asthma. The test can be performed at varying concentrations by varying the dose released from the inhaler. This overcomes the drawbacks of the methacholine challenge test of the prior art where several different solutions of methacholine at varying concentrations must be prepared. The prior art method is thus time consuming, prone to error and costly. In contrast, the method of the present invention can be self-administered or administered with very little supervision.

[0006] In one aspect, the present invention provides a formulation for use in detecting asthma comprising methacholine or histamine in a dry particulate form. The formulation is a dry powder methacholine or histamine formulation comprising composite particles of methacholine or histamine and a pharmaceutical grade sugar.

[0007] The formulation is a composite material comprising discrete particles which are a mixture of methacholine or histamine and, as carrier, a pharmaceutical grade sugar. Preferably the sugar is a regular grade and pharmaceutical grade sugar.

[0008] The methacholine or histamine are combined with the carrier in such a way that it will be delivered to the alveoli and lower airways of a person with the carrier. The composite particles of the formulation are formed in such a way that they have a median particle size to enable the methacholine to be conveyed on inhalation to the alveoli and lower airways of a person. Preferably the size of the particles in the formulation are from 0.1 μm to 10 μm, more

preferably from 2 μm to 8 μm, and most preferably from 2 μm to 5 μm.

[0009] The particles of the dry powder methacholine and histamine formulations may, for example, be spherical. The spherical particles may, for example, have a dimpled surface.

[0010] In another aspect, the present invention provides a method of preparing a methacholine or histamine formulation for use in detecting asthma comprising:

(a) combining methacholine or histamine, a pharmaceutical grade sugar and a liquid carrier to produce a flowable mixture; and,
(b) drying the flowable mixture at conditions to produce a composite material containing methacholine or histamine/sugar composite particles suitable for delivery to the alveoli and lower airways of a person.

[0011] In one embodiment the liquid carrier is water.

[0012] The flowable mixture is preferably dried by spray drying. In one embodiment the flowable mixture is atomized prior to being dried. The conditions under which the flowable mixture is spray dried is controlled to produce the desired particle size. In one embodiment the flowable mixture is preferably dried at conditions to form substantially spherical particles. More preferably, the flowable mixture is dried at conditions to form spherical particles which have a dimpled surface.

[0013] In another aspect, the present invention provides a methacholine or histamine formulation according to the invention for use in a method of detecting asthma in a person.

[0014] In a further aspect, the present invention provides the use of a methacholine or histamine formulation according to the invention for the manufacture of a preparation for detecting asthma. In this aspect, the person may inhale into his/her airways an effective amount of the methacholine or histamine formulation, and airway narrowing may be measured, for example by measuring the Forced Expiratory Volume in one second (FEV1), wherein a narrowing of the airways is diagnostic of asthma.

[0015] The methacholine or histamine formulation of the invention may be used in a method for detecting asthma in a person, the method comprising (a) having the person inhale an effective amount of the methacholine or histamine formulation in dry particulate form containing particles of respirable size and (b) measuring airway narrowing, wherein a narrowing of the airways is diagnostic of asthma.

[0016] An advantage of the present invention is that the particles produced by the method disclosed herein are well adapted for delivery to the alveoli and small airways of the lungs with minimal or no impact upon the throat or upper airways of the person, thus preferably resulting in no irratation.

[0017] In a further aspect, the present invention provides a dry powder composite particle consisting of methacholine and a pharmaceutical grade sugar, the particle having a size capable, on inhalation, of being delivered to the alveoli and lower airways of a person. Such dry powder composite particle may be used for the manufacture of a dry powder formulation for detecting asthma in a person. For example, in such use the person may inhale into his/her airways an effective amount of the dry powder formulation and airway narrowing may be measured, e.g. by measuring the Forced Expiratory Volume in one second (FEV1), wherein a narrowing of the airways is diagnostic of asthma.

[0018] Other objects, features and advantages of the present invention will become apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Methacholine Formulation

[0019] As hereinbefore mentioned, the present invention provides a methacholine or histamine formulation comprising methacholine or histamine in a dry particulate form for use in detecting asthma. The methacholine or histamine formulation is a composite material comprising discrete particles in a form suitable for inhalation by a user and which are a mixture of methacholine or histamine and, as carrier, a pharmaceutical grade sugar. Preferably, the sugar is lactose. In particular, the formulation comprises solid discrete flowable particles which may be entrained in the air inhaled by a person so as to travel to the alveoli and smaller airways of the lungs.

[0020] The particle size of the methacholine formulation is of a "respirable particle size" which is a size sufficient to enable the methacholine to be conveyed on inhalation to the alveoli and lower airways of a person. Preferably the particle will not settle out, impact or otherwise irritate the patient's throat. Preferably the size of the particles in the formulation are from 0.1 μm to 10 μm, more preferably from 2 μm to 8 μm and most preferably from 2 μm to 5 μm, based on mass median aerodynamic diameter (MMADD).

[0021] A person skilled in the art would understand that the sugar selected should be safe for inhalation. The sugar is preferably selected from lactose, dextrose, glucose, maltose, trehalose or combinations thereof and is most preferably lactose. The sugar may be a natural or a synthetic sugar and may include analogs or derivatives of sugars. The

sugar acts as a carrier and, therefore, any form of sugar approved as an excipient may be used. The sugar is of a pharmaceutical grade such as CP, USP, NF, BP, EP or BPC. The sugar should also be of a grade which results in the formation of the desired formulation. Preferably, the sugar should not be pre-treated or spray dried. Preferably, the sugar should be a "regular grade" sugar, such as preferably of a grade like \$310 Regular NF Lactose Monohydrate from Formost. The sugar which is used as a starting material is therefore in the form of a dry powder which is readily soluble in water.

[0022] The methacholine formulation of the present invention may be prepared by a method comprising:

(a) combining methacholine, a pharmaceutical grade sugar and a liquid carrier to produce a flowable mixture; and,
(b) drying the flowable mixture at conditions to produce a composite material containing methacholine / sugar composite particles suitable for delivery to the alveoli and lower airways of a person.

[0023] The methacholine may be any form of methacholine which is soluble in or miscible with the liquid carrier. For example, the methacholine may be a methacholine base. Alternately, or in addition, the methacholine may be a salt. The methachoine may be pharmacologically active analogs or derivatives of methacholine or substances which mimic the effect of methacholine, either alone or in combination with other active substances.

[0024] The liquid carrier is an agent which mixes with the sugar and the methacholine to a degree sufficient to form a flowable mixture. The liquid carrier may be any liquid or liquids with which the methacholine may be mixed and the sugar may be dissolved to form a flowable mixture which is preferably of a generally uniform composition. Methacholine bases are generally miscible in water and methacholine salt formulations are generally soluble in water. Further, sugars such as lactose are soluble in water. Accordingly, whether the methacholine is a base and/or a salt formulation, the liquid carrier may comprise water. When a salt is used, the liquid carrier solubilizes the methacholine and the sugar. When a methacholine base is used, the liquid carrier solubilizes the sugar and mixes with the liquid base to create a generally uniform solution (eg. it is miscible with the liquid base). While water is the preferred liquid carrier, other liquids in combination with or in place of water may be used. For example, alternate liquids may be used, either by themselves or in combination with water, to solubilize the solid material or to disperse the methacholine base in the liquid carrier.

[0025] In a further preferred embodiment, the liquid carrier may comprise a mixture of alcohol and water. The water and the alcohol form an azeotropic mixture. Methacholine base formulations are readily soluble in an alcohol. However, the lactose is not soluble in the alcohol. Pursuant to this embodiment, the flowable mixture may comprise less water thus assisting in the rate of drying of the flowable mixture and/or the amount of water in the dried product.

[0026] Preferably, the alcohol is a primary alcohol. Further, the alcohol is preferably a lower alkyl alcohol (i.e. C_1 to C_5). A particularly preferred alcohol which may used as a solvent for the methacholine base solution is ethanol. The ethanol may be CP grade, and preferably, is, USP grade. However, it will be appreciated that it is preferable, where possible, to avoid the use of alcohol in the base solution.

[0027] This liquid carrier preferably contains an excess amount of water compared to alcohol where alcohol is necessary as a cosolvent In such an embodiment, the mixture preferably comprises a minor proportion of alcohol and a major proportion of water. Where alcohol is required, the ratio of alcohol to water in the liquid carrier may be from about 1:1 to 1:10, and preferably from about 1:2 to 1:8.

[0028] The liquid carrier (eg. water) may be mixed with the methacholine to produce a liquid mixture to which the sugar may then be added. Accordingly, the sugar and a methacholine salt may be dissolved in water (or other suitable liquid carrier) to form the flowable mixture. Alternately, the sugar may be dissolved in water and the methacholine base may be mixed with the water to form the flowable mixture. It will be appreciated that the methacholine, liquid carrier and sugar may be combined together in any desired order to produce the dry flowable mixture.

[0029] According to the preferred embodiment of this invention, the methacholine compound is added to the water and mixed until a relatively consistent solution is achieved. Sugar is dissolved in water. Subsequently, the mixture of the methacholine in water is added to the aqueous sugar solution and mixed until the flowable product is produced. The mixing may be conducted by any means known in the art.

[0030] The amount of liquid mixture which is utilized is sufficient to produce a flowable mixture. Pursuant to the preferred embodiment, the mixture is finely divided (such as passing the flowable mixture through an orifice) on entry to a spray dryer, such as a Buchi-B191 Spray Dryer. The orifice is of a size which enables formation of particle sizes within the preferred ranges of the invention. The desired orifice size would be readily apparent to a person skilled in the art.

[0031] Accordingly, the flowable mixture is preferably in the form of a liquid or the like, which may readily be finely divided. In one embodiment the flowable mixture can be finely divided by passing the liquid through an atomizer (preferably a rotary atomizer) prior to drying.

[0032] The ratio of methacholine to sugar which is dissolved in the flowable mixture will vary upon the concentration of methacholine in the spray dried product. Due to product handling limitations, it is typical in the field that the carrier comprises a substantial portion of the weight of a powder formulation as compared to the active ingredient. The amount

of sugar which is utilized, compared to the amount of methacholine, must be sufficient such that the spray dried product can be used in association with dry powder inhalers which are known in the art. Accordingly, the ratio of methacholine to sugar in the flowable mixture may vary and is preferably from about 0.001:10 to about 10:0.001, more preferably from about 0.005:10 to about 1.5:10 and, most preferably, about 0.05:10 to about 1:10 parts by weight. Further, the concentration of methacholine in the flowable mixture may vary and is preferably from about 0.005 to about 1, more preferably from about 0.01 to about 0.6 and most preferably from about 0.01 to about 0.3 w/v (i.e. g/100 ml).

[0033] The flowable mixture is dried so as to produce particles which are sized so as to be able to travel to the alveoli and smaller airways of the lungs. Preferably, the particles have a particle size from about 0.1 μm to about 10 μm, more preferably from about 2 to about 8 μm and, most preferably from about 2.0 μm to about 5 μm based on the mass median aerodynamic diameter (MMAD) of the particles. The flowable mixture is preferably rapidly dried such as by using a spray drier. However, other drying techniques capable of producing appropriately sized particles (eg. the use of fluidized bed drying) may be used.

[0034] The flowable liquid is preferably rapidly dried so as to produce spherical or substantially spherical particles. Such particles may be achieved by using a rotary atomizer to feed the flowable liquid into a spray dryer or by passing the flowable liquid through a suitable sized orifice of a spray dryer which does not have a rotary atomizer, such as a Buchi-B 191 Spray Dryer.

[0035] The operating conditions of the spray dryer are adjusted so to produce particles which are sized so as to be able to travel to the alveoli and smaller airways of the lungs. If a rotary atomizer is used, the rotary atomizer may be operated at a liquid feed rate from about 2 to about 20, more preferably from 2 to about 10, and most preferably from about 2 to about 5 ml/min. The rotary atomizer may be operated from about 10,000 to about 30,000, more preferably from about 15,000 to about 25,000, and most preferably from about 20,000 to about 25,000 rpm.

[0036] The spray dryer is operated at temperatures sufficiently high to cause the liquid carrier to rapidly evolve without raising the temperature of the sugar and methacholine to a point at which these compounds commence to degrade. Accordingly, the spray dryer is preferably operated with an inlet temperature from about 120 to about 210°C, preferably from about 120 to about 170°C and more preferably at about 160°C, and an outlet temperature from preferably about 50 to about 130°C, or more preferably from about 50 to about 100°C, or more preferably from about 70 to about 100°C, and most preferably at about 81°C.

[0037] The medicament particles are spherical or of another aerodynamic shape. Such particles will tend not to aggregate when stored in a bulk form. Further, by evolving the liquid carrier sufficiently rapidly during the spray drying process, the medicament particles may be produced with an uneven or a "dimpled" surface. The uneven surface produces turbulence as the particles travel through the air, thus providing the particles with aerodynamic lift. This assists the particles to be entrained, and to remain entrained, in the air inhaled by a user thus improving the ability of the medicament particles to travel to the alveoli and smaller airways.

[0038] The final product (methacholine-lactose composite) contain various concentrations of methocholine as desired. It is preferably from about 0.1 to about 20%, more preferably from about 0.1 to about 10.5% and most preferably between about 0.5 to about 10% (wt/wt).

Histamine formulation

[0039] The above described method for preparing the methacholine formulations can be employed to prepare dry particulate formulations of histamine.

Method For Detecting Asthma

[0040] The novel methacholine and histamine formualtions of the present invention can be used in the detection of asthma. A method of detecting asthma utilising the methacholine or histamine formulations of the invention comprises (a) having the person inhale into his/her airways an effective amount of a methacholine or histamine formulation in dry particulate form containing particles of respirable size and (b) measuring airway narrowing, wherein a narrowing of the airways is diagnostic of asthma.

[0041] "Particulates of a respirable size" means particles that are able to be drawn into the airways of the person's lungs and will not settle out against the person's mouth or throat. Preferably the particles are form 0.1 μm to 10 μm, more preferably from 2 μm to 8 μm and most preferably from 2 μm to 5 μm, based on MMAD. The methacholine or histamine formulation contains a pharmaceutical grade sugar, more preferably lactose.

[0042] The methacholine or histamine formulation can be administered through a conventional dry powder inhaler which are compact, portable and easy to use. Breath activated inhalers having a housing, an air conduit adapted to conduct air flow to a patient, and means for introducing a medicament into the air conduit are generally known in the art, see, for example, U.S. Patent Serial No. 4,524,769 to Wetterlin; Bell et al., J. Pharmaceut. Sci. 60:1559, 1971 and Newman et al., Eur. Res. J. 2:247, 1989. Examples of suitable inhalers include SPINHALER®, TURBHALER®, RO-

TAHALER®, CYCLOHALER®, INHALATOR® and DISKHALER®. Breath activated inhalers differ from pressurized aerosol inhalers in that breath activated inhalers are activated by inhalation of the user so that the medicament is reliably drawn into the distal regions of the lung.

[0043] In order to perform the method for detecting asthma, the person being tested inhales the methacholine or histamine formulation from a breath activated inhaler. Preferably, the person is subjected to a series of tests, each at a higher dose of the methacholine or histamine. After each test the person will be tested for airway narrowing, preferably by measuring the Forced Expiratory Volume in one second (FEV1) using techniques known in the art. If airway narrowing is detected, then the person has asthma. Generally, if there is a 20% or greater reduction in the FEV1 compared with a baseline control then the person has asthma.

[0044] The following non-limiting examples are illustrative of the present invention

EXAMPLES

Example 1

Preliminary Tests for the Preparation of the Methacholine Formulation

1) Characterization of Materials received.

[0045] The material received was characterised using scanning Electron Microscope (SEM), to provide useful information for determining suitable composite formation conditions by spray drying.

2) Feasibility study for producing 2-5μm particles of Methacholine /Lactose composite powder.

[0046]

a) Drug powder of 5%wt/wt Methacholine in Lactose. Initial experiments indicated that spray drying technology is possible for producing spherical drug particles having a size range between 2 and 5μm from an aqueous solution. The adjustment of spraying operating conditions results in a strict particle size range. To meet the size requirements, droplets should have a narrow size distribution and a short residence time to avoid coagulation prior to drying. Experiments were conducted using a Laboratory spheroniser equipped with a rotary atomiser. Results are shown in Table 1. Note particle size was estimated from SEM. A more precise analysis would be obtained using thermogravimetric analysis (TGA) or x-ray diffraction (XRD) or laser diffraction.

3) Determination of appropriate spray drying conditions

[0047] Suitable spray drying conditions, including drying temperature, spinning speed of the atomiser wheel, solution feedrate and concentration of the solutes were determined experimentally to produce the composite powder according to required specifications. Results are listed in Tables 1 and 2.

Example 2

Preparation of methacholine Formulations

[0048] A number of methacholine formulations were prepared as indicated in Table 3. Methacholine and lactose in amounts listed in Table 3 were added to 485 grams of water . The mixture was stirred until the solution was clear (approximately 5 minutes). The mixture was spray dried in a Buchi Mini Spray Dryer -B 191, with an air flow rate of 600 ml/minute, and inlet and outlet temperature as indicated in Table 3. The methacholine and lactose solution was fed into the dryer at a flow rate setting as indicated in Table 3. The results are set out in Table 3.

[0049] Determination of Methacholine content in Methacholine-Lactose composite product was done using Capillary Electrophoresis (wavelength of detection = 214 nm), using standard methods known in the art. The acetyl-β-methacholine chloride in lactose methacholine was assayed using the following parameters:

Column: a 97 cm uncoated capillary 50 μm I.D. column
Wavelength: 214 nm
Indirect detection
Injection: 5 seconds
Voltage: 30kV

Buffer. 20mM Imidazole, pH 3.0
Capillary was rinsed with buffer for 2 minutes prior to injection

The buffer was prepared by dissolving 136 mg imidazole in 50 ml of water . The pH was then adjusted to 3.0 with 0.5 N HCL. Volume was then adjusted with water to 100 ml. The buffer was then filtered with a 0.45 μm filter. Acetyl-β-Methacholine Chloride (1mg/ml) standard was prepared by placing 100 mg of standard in 1000 ml of water.

[0050] Particle size was determined using SEM microscopy. It should be noted that sizes listed in Table 3 indicate an estimation of what all particle sizes in the formulation are under. A more precise measurement, using laser diffraction method would indicate that the median aerodynamic diameter (MMAD) of the particles were between about 2 to about 5 microns.

[0051] Methacholine formulations were prepared with 0.5, 2.0, 5.0 and 10%wt/wt methacholine in finished product (see example nos. 13-16 in Table 3). All the formulations showed good flowability. Example 12, which had a methacholine content in an amount higher than about 10% (i.e, above about 10.25%) in Methacholine-Lactose composite product, under the conditions used in Table 3 produced wet or very wet compound, which did not have the desired flowability for a dry powder inhaler. Varying the conditions may produce a final dry product with higher Methacholine concentrations.

[0052] Although a range of inlet and outlet temperatures of the spray drier could work, the optimal inlet temperature was 160°C, while the optimal outlet temperature of the spray dryer was 81°C, at a solution feed rate of 35%.

[0053] While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

[0054] All publications, patents and patent applications are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

TABLE 1

Test Matrix for the Determination of Suitable Spray Drying Conditions.							
	Drug Substance	Powder produced	T° drying (Centigrade)	rpm atomiser	feedrate (ml/min)	Solute %wt	Mean Size* (Micron)
1	Methacholine	Imp. 01	132	25500	10	14	32
2	methacholine	Imp. 02	126	25500	10	10	25
3	Methacholine	Imp. 03	135	25500	10	5	16
4	Methacholine	Imp.04	130	25500	10	3	6

*Estimated from SEM Micrographs

TABLE 2

Time	Exit Temperature ° C	Downstream heater temperature°C	Exhaust Temperature °C	Atomiser Air Pressure Kg/cm2
16.11	125	97	79.9	5.5
16.2	129	89	78.9	5.2
5.61	134	88	74.2	5.6
16.42	130	86	72.1	5.2
17	130	86	71.6	5.6
17.3	130	86	71.7	5.6
17.45	130	86	72.2	5.2
18.05	130	86	72.1	5.2
18.2	130	86	72.1	5.2
18.45	130	86	72.1	5.8

TABLE 2 (continued)

Time	Exit Temperature ° C	Downstream heater temperature°C	Exhaust Temperature °C	Atomiser Air Pressure Kg/ cm2
19.05	130	86	72	5.2

TABLE 3

EXPERIMENTAL PART FOR PREPARATION OF METHACHOLINE-LACTOSE COMPOSITE PRODUCT

No.	Methacholine added (g)	Lactose added (g)	Water added (g)	Methacholine: Lactose ratio	Methacholine concentration in solution % (w/v)	Air Flow ml/min	Solution Feed Rate %	Inlet Temp (°C)	Outlet Temp (°C)	Particle Size (μ)	Methacholine concentration in Finished Product %(w/w)	Description of powder
1	0.9125	14.1025	485	0.0647	0.1881	600	35	130	51	not done	not done	dry
2	0.9125	14.1025	485	0.0647	0 1881	600	35	160	69	not done	not done	very wet
3	0.9125	14.1025	485	0.0647	0.1881	600	24	160	86	not done	not done	dry
4	0 9146	14.1068	485	0.0648	0.1886	600	35	130	57	< 6	6.45	dry
5	0 9146	14.1068	485	0.0648	0.1886	600	35	160	81	< 7	6.48	dry
6	0.9146	14.1068	485	0.0648	0.1886	600	35	190	98	< 8	6.56	dry
7	0.9146	14.1068	485	0.0648	0.1886	600	18	190	116	< 7	not done	dry
8	1 8250	14.1025	485	0.1294	0.3763	600	24	160	86	not done	not done	very wet
9	1 8250	14.1025	485	0.1294	0.3763	600	24	190	103	not done	not done	very wet
10	1.8230	14.1128	485	0.1291	0.3759	600	18	190	119	not done	not done	wet
11	1 8230	14.1128	485	0.1291	0.3759	600	18	203	127	not done	not done	very wet
12	1.8230	14.1128	485	0.1291	0.3759	600	35	160	81	not done	12.76	very wet
13	0.0700	14.0000	485	0.0050	0.0144	600	35	160	81	< 8	0.57	dry
14	0.2800	14.000	485	0.0200	0.0577	600	35	160	81	< 6	2.23	dry
15	0.7000	14.0000	485	0.0500	0.1443	600	35	160	81	< 6	4.97	dry
16	1.4000	14.000	485	0.1000	0.2887	600	35	160	81	< 7	10.23	dry

Claims

1. A dry powder methacholine formulation comprising composite particles of methacholine and a pharmaceutical grade sugar.

2. The formulation according to claim 1 wherein the composite particles are of a size capable, on inhalation, of being delivered to the alveoli and lower airways of a person.

3. The formulation according to claim 1 or claim 2 wherein the sugar is lactose.

4. The formulation according to claim 3 wherein the particles are about 0.1 μm to about 10 μm in size.

5. The formulation according to claim 4 wherein the particles are about 2 μm to about 8 μm in size.

6. The formulation according to claim 5 wherein the particles are about 2 μm to about 5 μm in size.

7. The formulation according to claim 6 wherein the particles are spherical.

8. The formulation according to claim 7 wherein the particles have a dimpled surface.

9. The formulation according to claim 6 wherein the amount of methacholine is from about 0.1 to about 10.5% wt/wt.

10. A methacholine formulation according to any one of claims 1 to 9 for use in a method of detecting asthma in a person.

11. Use of a methacholine formulation according to any one of claims 1 to 9 for the manufacture of a preparation for detecting asthma in a person.

12. Use according to claim 11, wherein the person inhales into his/her airways an effective amount of the methacholine formulation, and airway narrowing is measured, wherein a narrowing of the airways is diagnostic of asthma.

13. Use according to claim 12, wherein airway narrowing is measured by measuring the Forced Expiratory Volume in one second (FEV1).

14. A method of preparing a methacholine formulation comprising:

    (a) combining methacholine, a pharmaceutical grade sugar and a liquid carrier to produce a flowable mixture; and
    (b) drying the flowable mixture to produce a composite material at conditions to produce methacholine/sugar composite particles suitable for delivery to the alveoli and lower airways of a person.

15. The method according to claim 14 wherein the pharmaceutical grade sugar is lactose.

16. The method according to claim 15 wherein the liquid carrier is water.

17. The method according to claim 16, wherein the ratio of lactose to methacholine in the flowable mixture is from about 0.001:10 to about 10:0.0001 parts by weight and the concentration of methacholine varies from about 0.005 to about 1% w/v.

18. The method according to claim 14, wherein the flowable mixture is spray dried.

19. The method according to claim 18, wherein the temperature of the spray drier at the inlet is between about 120 to about 170°C and the temperature at the outlet is between about 50 to about 100°C.

20. A dry powder histamine formulation comprising composite particles of histamine and a pharmaceutical grade sugar.

21. The formulation according to claim 20 wherein the composite particles are of a size capable, on inhalation, of being delivered to the alveoli and lower airways of a person.

22. The formulation according to claim 20 or claim 21 wherein the sugar is lactose.

23. The formulation according to claim 22 wherein the particles are about 0.1 μm to about 10 μm in size.

24. The formulation according to claim 23 wherein the particles are about 2 μm to about 8 μm in size.

25. The formulation according to claim 24 wherein the particles are about 2 μm to about 5 μm in size.

26. The formulation according to claim 25 wherein the particles are spherical.

27. The formulation according to claim 26 wherein the particles have a dimpled surface.

28. The formulation of claim 24 wherein the amount of histamine is from about 0.1 to 10.5% wt/wt.

29. A histamine formulation according to any one of claims 20 to 28 for use in a method of detecting asthma in a person.

30. Use of a histamine formulation according to any one of claims 20 to 28 for the manufacture of a preparation for detecting asthma in a person.

31. Use according to claim 30, wherein the person inhales into his/her airways an effective amount of the histamine formulation, and airway narrowing is measured, wherein a narrowing of the airways is diagnostic of asthma.

32. Use according to claim 31, wherein airway narrowing is measured by measuring the Forced Expiratory Volume in one second (FEV1).

33. A method of preparing a histamine formulation comprising:

(a) combining histamine, a pharmaceutical grade sugar and a liquid carrier to produce a flowable mixture; and
(b) drying the flowable mixture to produce a composite material at conditions to produce histamine/sugar composite particles suitable for delivery to the alveoli and lower airways of a person.

34. The method according to claim 33 wherein the pharmaceutical grade sugar is lactose.

35. The method according to claim 34, wherein the liquid carrier is water.

36. The method according to claim 35, wherein the ratio of lactose to histamine in the flowable mixture is from about 0.001:10 to about 10:0.0001 parts by weight and the concentration of histamine varies from about 0.005 to about 1% w/v.

37. The method according to claim 33, wherein the flowable mixture is spray dried.

38. The method according to claim 37, wherein the temperature of the spray drier at the inlet is between 120 to about 170°C and the temperature at the outlet is between 50 to about 100°C.

39. A dry powder composite particle consisting of methacholine and a pharmaceutical grade sugar, the particle having a size capable, on inhalation, of being delivered to the alveoli and lower airways of a person

40. Use of a dry powder composite particle according to claim 39 for the manufacture of a dry powder formulation for detecting asthma in a person.

41. Use according to claim 40 wherein the person inhales into his/her airways an effective amount of the dry powder formulation and airway narrowing is measured, wherein a narrowing of the airways is diagnostic of asthma.

42. Use according to claim 41 wherein airway narrowing is measured by measuring the Forced Expiratory Volume in one second (FEV1).

Patentansprüche

1. Methacholin-Trockenpulverformulierung, die zusammengesetzte Teilchen von Methacholin und eines Zuckers pharmazeutischer Reinheit umfaßt.

2. Formulierung nach Anspruch 1, worin die zusammengesetzten Teilchen eine Größe haben, die beim Inhalieren an die Alveolen und unteren Luftwege einer Person abgegeben werden kann.

3. Formulierung nach Anspruch 1 oder Anspruch 2, worin der Zucker Laktose ist.

4. Formulierung nach Anspruch 3, worin die Teilchen eine Größe von etwa 0,1 μm bis etwa 10 μm haben.

5. Formulierung nach Anspruch 4, worin die Teilchen eine Größe von etwa 2 μm bis etwa 8 μm haben.

6. Formulierung nach Anspruch 5, worin die Teilchen eine Größe von etwa 2 μm bis etwa 5 μm haben.

7. Formulierung nach Anspruch 6, worin die Teilchen kugelförmig sind.

8. Formulierung nach Anspruch 7, worin die Teilchen eine mit Vertiefungen versehene Oberfläche haben.

9. Formulierung nach Anspruch 6, bei der die Menge an Methacholin etwa 0,1 bis etwa 10,5 % (Gewicht/Gewicht) ist.

10. Methacholin-Formulierung nach einem der Ansprüche 1 bis 9 zur Verwendung in einem Verfahren zur Ermittlung von Asthma bei einer Person.

11. Verwendung einer Methacholin-Formulierung nach einem der Ansprüche 1 bis 9 zur Herstellung eines Präparats zur Ermittlung von Asthma bei einer Person.

12. Verwendung nach Anspruch 11, worin die Person eine wirksame Menge der Methacholin-Formulierung in ihre Luftwege inhaliert, wobei eine Verengung der Luftwege ein Diagnostikum für Asthma ist.

13. Verwendung nach Anspruch 12, worin die Luftwegeverengung durch Messung des erzwungenen Ausatmungsvolumens in einer Sekunde (FEV1) gemessen wird.

14. Verfahren zur Herstellung einer Methacholin-Formulierung, bei dem man:

    a) Methacholin, einen pharmazeutisch reinen Zucker und einen flüssigen Träger zur Erzeugung eines fließfähigen Gemisches miteinander vereinigt und

    b) das fließfähige Gemisch trocknet und so ein zusammengesetztes Material bei Bedingungen erzeugt, die für die Abgabe an die Alveolen und unteren Luftwege einer Person geeignet sind.

15. Verfahren nach Anspruch 14, bei dem der pharmazeugisch reine Zucker Laktose ist.

16. Verfahren nach Anspruch 15, bei dem der flüssige Träger Wasser ist.

17. Verfahren nach Anspruch 16, bei dem das Verhältnis von Laktose zu Methacholin in dem fließfähigen Gemisch etwa 0,001:10 bis etwa 10:0,0001 Gewichtsteile umfaßt und die Methacholin-Konzentration von etwa 0,005 bis etwa 1 % (Gewicht/Volumen) variiert.

18. Verfahren nach Anspruch 14, bei dem das fließfähige Gemisch sprühgetrocknet wird.

19. Verfahren nach Anspruch 18, bei dem die Temperatur des Sprühtrockners am Einlaß zwischen etwa 120 und etwa 170°C beträgt und die Temperatur am Auslaß zwischen etwa 50 und etwa 100°C beträgt.

20. Trockenpulver-Histamin-Formulierung, die zusammengesetzte Teilchen von Histamin und eines pharmazeutisch reinen Zuckers umfaßt.

21. Formulierung nach Anspruch 20, worin die zusammengesetzten Teilchen eine Größe haben, die beim Inhalieren an die Alveolen und unteren Luftwege einer Person abgegeben werden können.

22. Formulierung nach Anspruch 20 oder Anspruch 21, worin der Zucker Laktose ist.

23. Formulierung nach Anspruch 22, worin die Teilchen etwa 0,1 μm bis etwa 10 μM groß sind.

24. Formulierung nach Anspruch 23, worin die Teilchen eine Größe von etwa 2 μM bis etwa 8 μM haben.

25. Formulierung nach Anspruch 24, worin die Teilchen eine Größe von etwa 2 μM bis etwa 5 μM haben.

26. Formulierung nach Anspruch 25, worin die Teilchen kugelförmig sind.

27. Formulierung nach Anspruch 26, worin die Teilchen eine Oberfläche mit Vertiefungen haben.

28. Formulierung nach Anspruch 24, worin die Histaminmenge etwa 0,1 bis 10,5% (Gewicht/Gewicht) hat.

29. Histamin-Formulierung nach einem der Ansprüche 20 bis 28 für die Verwendung in einem Verfahren zur Ermittlung von Asthma bei einer Person.

30. Verwendung einer Histamin-Formulierung nach einem der Ansprüche 20 bis 28 zur Herstellung eines Präparats für die Ermittlung von Asthma bei einer Person.

31. Verwendung nach Anspruch 30, wobei die Person eine wirksame Menge der Histamin-Formulierung in ihre Luftwege inhaliert und die Verengung der Luftwege gemessen wird, wobei eine Verengung der Luftwege ein Diagnostikum für Asthma ist.

32. Verwendung nach Anspruch 31, bei der die Luftwegeverengung durch Messung des erzwungenen Ausatmungsvolumens in einer Sekunde (FEV1) gemessen wird.

33. Verfahren zur Herstellung einer Histamin-Formulierung, bei dem man

a) Histamin, einen pharmazeutisch reinen Zucker und einen flüssigen Träger miteinander vereinigt, um ein fließfähiges Gemisch zu erzeugen und

b) das fließfähige Gemisch trocknet, um ein zusammengesetztes Material bei Bedingungen zu erzeugen, bei denen zusammengesetzte Histamin/Zuckerteilchen erzeugt werden, die für die Abgabe an die Alveolen und unteren Luftwege einer Person geeignet sind.

34. Verfahren nach Anspruch 33, bei dem der pharmazeutisch reine Zucker Laktose ist.

35. Verfahren nach Anspruch 34, bei dem der flüssige Träger Wasser ist.

36. Verfahren nach Anspruch 35, bei dem das Verhältnis von Laktose zu Histamin in dem fließfähigen Gemisch etwa 0,001:10 bis etwa 10:0,0001 Gewichtsteile ist und die Histaminkonzentration von etwa 0,005 bis etwa 1 % (Gewicht/Volumen) variiert.

37. Verfahren nach Anspruch 33, bei dem das fließfähige Gemisch sprühgetrocknet wird.

38. Verfahren nach Anspruch 37, bei dem die Temperatur des Sprühtrockners an dem Einlaß zwischen 120 und etwa 170°C und die Temperatur am Auslaß zwischen 50 und etwa 100°C liegt.

39. Zusammengesetztes Trockenpulverteilchen, das aus Methacholin und einem pharmazeutisch reinen Zucker besteht, wobei die Teilchen eine Größe haben, die beim Inhalieren an die Alveolen und unteren Luftwege einer Person abgegeben werden können.

40. Verwendung eines zusammengesetzten Trockenpulverteilchens nach Anspruch 39 für die Herstellung einer Trokkenpulverformulierung zur Ermittlung von Asthma bei einer Person.

41. Verwendung nach Anspruch 40, bei der die Person eine wirksame Menge der Trockenpulverformulierung in ihre Luftwege inhaliert und die Verengung der Luftwege gemessen wird, wobei eine Verengung der Luftwege ein Diagnostikum für Asthma ist.

42. Verwendung nach Anspruch 41, bei der die Verengung der Luftwege durch Messung des erzwungenen Ausatmungsvolumens in einer Sekunde (FEV1) gemessen wird.

Revendications

1. Formulation de méthacholine en poudre sèche, comprenant des particules composites de méthacholine et un sucre de qualité pharmaceutique.

2. Formulation suivant la revendication 1, dans laquelle les particules composites ont des dimensions leur permettant, par inhalation, d'être délivrées aux alvéoles et aux voies aériennes inférieures d'une personne.

3. Formulation suivant la revendication 1 ou la revendication 2, dans laquelle le sucre est le lactose.

4. Formulation suivant la revendication 3, dans laquelle les particules ont des dimensions d'environ 0,1 μm à environ 10 μm.

5. Formulation suivant la revendication 4, dans laquelle les particules ont des dimensions d'environ 2 μm à environ 8 μm.

6. Formulation suivant la revendication 5, dans laquelle les particules ont des dimensions d'environ 2 μm à environ 5 μm.

7. Formulation suivant la revendication 6, dans laquelle les particules sont sphériques.

8. Formulation suivant la revendication 7, dans laquelle les particules ont une surface munie de fossettes.

9. Formulation suivant la revendication 6, dans laquelle la quantité de méthacholine est comprise dans l'intervalle d'environ 0,1 à environ 10,5 % en poids/poids.

10. Formulation de méthacholine suivant l'une quelconque des revendications 1 à 9, destinée à être utilisée dans une méthode de détection de l'asthme chez une personne.

11. Utilisation d'une formulation de méthacholine suivant l'une quelconque des revendications 1 à 9 pour la production d'une préparation destinée à la détection de l'asthme chez une personne.

12. Utilisation suivant la revendication 11, dans laquelle la personne inhale dans ses voies aériennes une quantité efficace de la formulation de méthacholine, et le rétrécissement des voies aériennes est mesuré, un rétrécissement des voies aériennes étant un diagnostic de l'asthme.

13. Utilisation suivant la revendication 12, dans laquelle le rétrécissement des voies aériennes est mesuré en mesurant le volume expiratoire forcé en une seconde (FEV1).

14. Procédé pour la préparation d'une formulation de méthacholine, comprenant :

    (a) l'association de méthacholine, d'un sucre de qualité pharmaceutique et d'un véhicule liquide pour produire un mélange apte à l'écoulement ; et
    (b) le séchage du mélange apte à l'écoulement pour produire une matière composite dans des conditions permettant de produire des particules composites de méthacholine/sucre convenables pour être délivrées aux alvéoles et aux voies aériennes inférieures d'une personne.

15. Procédé suivant la revendication 14, dans lequel le sucre de qualité pharmaceutique est le lactose.

16. Procédé suivant la revendication 15, dans lequel le véhicule liquide est l'eau.

17. Procédé suivant la revendication 16, dans lequel le rapport du lactose à la méthacholine dans le mélange apte à l'écoulement est compris dans l'intervalle d'environ 0,001:10 à environ 10:0,0001 parties en poids, et la concentration de méthacholine varie dans l'intervalle d'environ 0,005 à environ 1 % en poids/volume.

18. Procédé suivant la revendication 14, dans lequel le mélange apte à l'écoulement est séché par pulvérisation.

19. Procédé suivant la revendication 18, dans lequel la température de l'appareil de séchage par pulvérisation à l'orifice d'admission est comprise dans l'intervalle d'environ 120 à environ 170°C et la température à l'orifice de sortie est comprise dans l'intervalle d'environ 50 à environ 100°C.

20. Formulation d'histamine en poudre sèche comprenant des particules composites d'histamine et un sucre de qualité pharmaceutique.

21. Formulation suivant la revendication 20, dans laquelle les particules composites ont des dimensions leur permettant, par inhalation, d'être délivrées aux alvéoles et aux voies aériennes inférieures d'une personne.

22. Formulation suivant la revendication 20 ou la revendication 21, dans laquelle le sucre est le lactose.

23. Formulation suivant la revendication 22, dans laquelle les particules ont des dimensions d'environ 0,1 μm à environ 10 μm.

24. Formulation suivant la revendication 23, dans laquelle les particules ont des dimensions d'environ 2 pm à environ 8 μm.

25. Formulation suivant la revendication 24, dans laquelle les particules ont des dimensions d'environ 2 μm à environ 5 μm.

26. Formulation suivant la revendication 25, dans laquelle les particules sont sphériques.

27. Formulation suivant la revendication 26, dans laquelle les particules ont une surface présentant des fossettes.

28. Formulation suivant la revendication 24, dans laquelle la quantité d'histamine est comprise dans l'intervalle d'environ 0,1 à 10,5 % en poids/poids.

29. Formulation d'histamine suivant l'une quelconque des revendications 20 à 28, destinée à être utilisée dans une méthode de détection de l'asthme chez une personne.

30. Utilisation d'une formulation d'histamine suivant l'une quelconque des revendications 20 à 28 pour la production d'une préparation destinée à la détection de l'asthme chez une personne.

31. Utilisation suivant la revendication 30, dans laquelle la personne inhale dans ses voies aériennes une quantité efficace de la formulation d'histamine, et le rétrécissement des voies aériennes est mesuré, un rétrécissement des voies aériennes étant un diagnostic de l'asthme.

32. Utilisation suivant la revendication 31, dans laquelle le rétrécissement des voies aériennes est mesuré en mesurant le volume expiratoire forcé en une seconde (FEV1).

33. Procédé pour la préparation d'une formulation d'histamine, comprenant :

(a) l'association d'histamine, d'un sucre de qualité pharmaceutique et d'un véhicule liquide pour produire un mélange apte à l'écoulement ; et
(b) le séchage d'un mélange apte à l'écoulement pour produire une matière composite dans des conditions permettant de produire des particules composites d'histamine/sucre convenables pour être délivrées aux alvéoles et aux voies aériennes inférieures d'une personne.

34. Procédé suivant la revendication 33, dans lequel le sucre de qualité pharmaceutique est le lactose.

35. Procédé suivant la revendication 34, dans lequel le véhicule liquide est l'eau.

36. Procédé suivant la revendication 35, dans lequel le rapport du lactose à l'histamine dans le mélange apte à l'écoulement est compris dans l'intervalle d'environ 0,001:10 à environ 10:0,0001 parties en poids, et la concentration d'histamine varie dans l'intervalle d'environ 0,005 à environ 1 % en poids/volume.

37. Procédé suivant la revendication 33, dans lequel le mélange apte à l'écoulement est séché par pulvérisation.

38. Procédé suivant la revendication 37, dans lequel la température de l'appareil de séchage par pulvérisation à l'orifice d'admission est comprise dans l'intervalle de 120 à environ 170°C et la température à l'orifice de sortie est comprise dans l'intervalle de 50 à environ 100°C.

39. Particule composite de poudre sèche, consistant en méthacholine et un sucre de qualité pharmaceutique, la particule ayant des dimensions lui permettant, par inhalation, d'être délivrée aux alvéoles et aux voies aériennes inférieures d'une personne.

40. Utilisation d'une particule composite de poudre sèche suivant la revendication 39 pour la production d'une formulation en poudre sèche pour la détection de l'asthme chez une personne.

41. Utilisation suivant la revendication 40, dans laquelle la personne inhale dans ses voies aériennes une quantité efficace de la formulation en poudre sèche et le rétrécissement des voies aériennes est mesuré, un rétrécissement des voies aériennes étant un diagnostic de l'asthme.

42. Utilisation suivant la revendication 41, dans laquelle le rétrécissement des voies aériennes est mesuré en mesurant le volume expiratoire forcé en une seconde (FEV1).